Common Polygenic Variation Contributes to Risk of Migraine in the Norfolk Island Population

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Abstract

Migraine has been defined as a common disabling primary headache disorder. Epidemiology studies have provided with the undeniable evidence of genetic components as active players in the development of the disease under a polygenic model in which multiple risk alleles exert modest individual effects. Our objective was to test the contribution of a polygenic effect to migraine risk in the Norfolk Island population using a panel of SNPs reported to be disease associated in published migraine GWAS. We also investigated whether individual SNPs were associated with gene expression levels measured in whole-blood. Polygenic scores were calculated in a total of 285 related individuals (74 cases, 211 controls) from the Norfolk Island using 51 SNPs previously reported to be associated with migraine in published GWAS. The association between polygenic score and migraine case-control status was tested using logistic regression. Results indicate that a migraine polygenic risk score was associated with migraine case-control status in this population (P=0.016). This supports the hypothesis that multiple SNPs with weak effects collectively contribute to migraine risk in this population. Amongst the SNPs included in the polygenic model, 4 were associated with the expression of the *USMG5* gene, including rs171251 (P = 0.012). Results from this study provide evidence for a polygenic contribution to migraine risk in an isolated population and highlight specific SNPs that regulate the expression of *USMG5*, a gene critical for mitochondrial function.

Keywords: migraine, polygenic score, eQTL analysis, genetic isolate, USMG5.

## Introduction

Migraine is a common disabling primary headache disorder, classified into two major groups, migraine without aura (MO) and migraine with aura (MA) (Levin 2013). MO is the most common form with headache attacks lasting between 4-72 hours. In addition, MA sufferers often experience aural symptoms preceding the headache phase of the migraine episode.

Although the pathophysiology of migraine is not very well understood, epidemiological studies have convincingly demonstrated that genetic components contribute to the development of the disease. Genetic risk variants have been identified in studies of Familial Hemiplegic Migraine (FMH), a monogenic form of MA; specifically, risk variants in/near *CACNA1A*, *ATP1A2* and *SCNA1A* (Ophoff, Terwindt et al. 1996, Ambrosini, D'Onofrio et al. 2005, Dichgans, Freilinger et al. 2005). Additional common risk variants have been identified through Genome-Wide Association Studies (GWAS), namely rs9908234 (Ligthart, de Vries et al. 2011) in *NGFR*, rs1835740 (Ligthart, de Vries et al. 2011, Anttila, Winsvold et al. 2013) near *PGCP*, rs2651899 (*PRDM16*), rs10166942 (*TRPM8*) and rs11172113 (LRP1) (Chasman, Schurks et al. 2011). However, the replication of these variants in other populations has been challenging (Silberstein and Dodick 2013), as has been the identification of new migraine risk variants.

Genetic studies of isolated populations, such as that of Norfolk Island, provide improved power to identify genetic risk variants (Jorde, Watkins et al. 2000). Despite this, genetic studies of migraine in the Norfolk Island have failed to identify risk variants with large effects on disease risk (Cox, Lea et al. 2012, Maher, Lea et al. 2012, Rodriguez-Acevedo, Maher et al. 2013). This suggests that in this isolated population, the genetic contribution to migraine risk might be mostly determined by the combined effect of many risk variants with small effects. The aim of this study was to test this possibility by estimating a migraine polygenic risk score for individuals in the Norfolk Island based on SNPs identified in published GWAS and then testing its association with disease status.

Methods

*Population assessment*

Norfolk Island belongs to the Commonwealth of Australia and it is located off the eastern coast, approximately 1700 km northeast of Sydney, on the Norfolk Ridge. The modern Norfolk Island (NI) population comes from a settlement of 194 inhabitants resettled from Pitcairn Island in 1856 all descendants of nine male "Bounty" mutineers and twelve Tahitian women (Bellis, Cox et al. 2008). Since that time, the island has been isolated and strict immigration and quarantine legislation restricts migration to Norfolk. Thus, of the approximately 1200 current permanent residents, up to 80% can trace their heritage back to the Island's initial founders. The heritability of migraine in this population has been estimated to be 0.53 (Cox, Lea et al. 2012).

Phenotypic data and biological specimens (venous blood) were obtained from 600 subjects (261 males, 339 females). DNA was isolated using a standard salting-out procedure (Miller, Dykes et al. 1988). Phenotypic data was obtained via a medical questionnaire that surveyed migraine family history, symptoms, triggers, and medication use. An in depth interview and comprehensive medical questionnaire was undertaken on all individuals and used to obtain phenotypic data, including migraine information regarding family history, symptoms, triggers and medication. Migraine diagnosis was in accordance with ICHD-II guidelines. The inclusion criteria used to select cases was a diagnostic of MA or MO with other non-migraineurs included in the control population. Genealogical data were obtained from multiple sources, including questionnaire, municipal and historical records. Because all the individuals share a common genetic background and under the hypothesis of a common major variant, all individuals diagnosed with subtypes MA or MO were grouped together and phenotyped as being affected with migraine. The study protocol was initially approved by the Griffith University Human Research Ethics Committee and subsequently by the Queensland University of Technology Human Research Ethics Committee. All subjects provided signed, informed consent prior to participation.

*Genome-wide SNP genotyping*

DNA samples from the Norfolk Island Population were genotyped according to the manufacturer's instructions on the Illumina Infinium High Density (HD) Human610-Quad DNA analysis BeadChip

version 1. A total of 620,901 genome wide markers were genotyped in a sub-sample of 285 related individuals (74 cases: 22 males and 52 females; and 211 controls: 114 males and 97 females). Twenty-eight selected samples (5% of both cases and controls) were repeated to ensure concordance and accuracy of genotyping. Samples were scanned on the Illumina BeadArray 500GX Reader. Raw data was obtained using Illumina BeadScan image data acquisition software (Version 2.3.0.13).

*SNPs selection and score calculation*

We used the Gene Central Database (Beck, Hastings et al. 2014) to select genetic variants previously associated with migraine in published GWAS. Using genotype data from Europeans of the HapMap project (International HapMap, Altshuler et al. 2010), we reduced this list of SNPs to an independent set ($r^2$<0.1) of 51 variants using PLINK (Purcell, Neale et al. 2007) (Supplemental Table 1). Of note, each of these SNPs had previously been individually tested for association with migraine risk in the Norfolk Island population, with none having a significant (P<0.05) association (Cox, Lea et al. 2012).

These 51 SNPs were used to calculate a migraine polygenic score in PLINK (Purcell, Neale et al. 2007). The weight attributed to each SNP corresponded to the beta coefficient (β) reported in previous studies (Supplemental Table 1). Initially, the covariates age, sex and kinship were individually tested for association with migraine and only the significantly (P-value < 0.05) associated covariates were included in the final logistic regression model where the multiple allele score was set as a predictable variable and the migraine phenotype was set as the independent variable. In secondary analyses, the polygenic risk score was also dichotomised to compare the risk of disease between the bottom and top 25% percentiles of the polygenic risk score distribution (Figure 1).

*Genome-wide expression*

Sample collection has been previously described (Benton, Lea et al. 2013). Expression profiling was performed with the HumanHT-12 v.4 Expression BeadChip Kit (Illumina) for a total number of 335 individuals (79 cases and 256 controls). Array images were scanned on the Illumina iScan and analyzed initially with the Gene Expression Module from GenomeStudio (v.2011.1). Background subtraction was

applied, and missing bead types were imputed with GenomeStudio. On the basis of the number of expressed probes (at "detection P values" $\leq 0.05$), mean raw expression values across probes, and correlations between samples, all samples, with the exception of one, provided high-quality data. The sample with low-quality data was removed. Significantly expressed probes were then determined at a false-discovery rate of 5%. Subsequently, the raw expression levels of probes detecting significant expression were shifted by a constant amount so that the minimum observed value of any probe in any sample was 1.0; this was followed by $\log_2$ transformation and quantile normalization.

*eQTL analysis*

A total of 279 samples (72 cases and 207 controls) with both genotypic and levels of gene expression data were included in the analysis. Transcripts within 1Mb of distance from each of the 51 SNPs included in the polygenic model were selected for analysis using the University of California Santa Cruz (UCSC) table browser data retrieval web tool (Karolchik, Hinrichs et al. 2004). We used linear regression to test the association between individual SNPs (coded additively) and gene transcription levels of genes located within 1Mb of each SNP. Genotypes were coded as 0, 1 or 2 according to the copies of a reference allele. In this study, the reference allele was the allele with the minor allele frequency (MAF). Gene-dropping simulations under the null hypothesis of no association were used to correct for multiple testing. Specifically, empirical P-values were obtained for each SNP after correcting the observed asymptotic P-value for the number of genes tested for that SNP ("locus-wide" correction) and for all the SNPs and genes tested in the analysis (a total of 418 tests; "study-wide" correction). Briefly, for each simulation, we (1) used Merlin (Abecasis, Cherny et al. 2002) to generate random genotypes for the 51 SNPs for the 279 related individuals; (2) tested each simulated SNP for association with the observed expression levels of the nearby genes, as in the real dataset; and (3) retained the most significant P-value for each SNP across all genes tested (for "locus-wide" correction) and the most significant P-value across all tests performed (for "study-wide" correction). This procedure was repeated 1000 times, and the retained simulated P-values used to correct the observed asymptotic P-values for multiple-testing.

Results

*Polygenic score*

We identified 140 SNPs previously reported to be associated with migraine in published GWAS, including a set of 51 SNPs in low linkage disequilibrium ($r^2$<0.1) with each other (Supplemental Table 1). Individually, all 51 SNPs were not significantly associated with the risk of migraine in the Norfolk Island population (Cox, Lea et al. 2012). We reasoned that if some of these were indeed true risk factors with small effects on migraine susceptibility, then a polygenic risk score that aggregated the effects of all 51 SNPs would be significantly associated with disease status. To test this possibility, we used the association beta coefficient values reported by published migraine GWAS (Supplemental data 1) to generate a polygenic risk score across all 51 SNPs per individual. We found that this polygenic score was significantly and positively associated with migraine case-control status (P=0.016); cases had a higher load of risk alleles when compared to controls (Figure 1). Individuals in the top 25% of the polygenic score distribution were 3.1-fold (CI=1.37-7.55, P=0.008) more likely to be affected by migraine than individuals in the bottom 25% of the distribution (Figures 2 and 3).

**Fig.1** Scores vs Migraine boxplot distribution. This figure shows the boxplot distribution of the scores in the controls and the cases in the Norfolk Island Population. A significant P-value (0.016) was obtained after testing migraine and score correlation using a logistic regression model

**Fig.2** Histogram of Scores. Scores were calculated for all individuals in the population. Individuals with extreme scores are indicated by grey (scores ≤ 0.003) and black (scores ≥ 0.02) bars. A logistic regression analysis showed that higher scores are more frequently present in migraine cases than in healthy controls (P-value = 0.008 ; OR = 3.11; CI=1.37-7.55)

**Fig.3** Bar plot for the score frequencies. The frequency of higher scores (≥0.02) (black), lower scores (≤0.003) (grey) and intermediate scores (0.02≥ scores ≤ 0.003) (white) among cases and controls shows a statistically significant difference ($\chi 2$ = 6.81; P-value=0.0009; OR=2.94; CI= 1.28 to 6.73) in their distribution, which suggests that migraine sufferers tend to have a higher genetic load of risk alleles than their respective controls

*eQTL analysis*

In order to evaluate the potential biological role played by these 51 SNPs, we tested the association between each SNP and the expression levels of nearby genes. A total of 1347 genes were located within 1Mb of one of the 51 SNPs. However, expression levels for only 327 of these genes were available in the Illumina array used, being represented by 337 probes. Results showed that 10 SNPs were significantly associated with the expression of a nearby gene after a locus-wide correction for the number of genes tested for each SNP (Table 1). Of these, the association for 4 SNPs remained significant after a study-wide correction for multiple testing (Figure 4): rs1712517 with USMG5 (corrected P=0.012); rs11172113 with STAT6 (P=0.033); rs11906854 with *CPNE1* (P=0.044); and rs4803455 with BCKDHA (P=0.044). The predicted biological functions for these genes are listed in Table 2. For USMG5 and STAT6, the allele that increased migraine risk was associated with increased gene expression, whereas the reverse was observed for *CPNE1* and *BCKDHA* (Figure 3). We additionally tested the correlation between the levels of transcription of these eQTL genes and migraine status and no significant p-value ($p \leq 0.05$) was detected.

**Fig.4** Genotype vs Levels of expression Boxplot Distribution. a. rs1712517 vs USMG5;b. rs11172113 vs STAT6;c. rs11906854 vs CPNE1; d. rs4803455 vs BCKDHA. Significant eQTLs (S_P-value ≤ 0.05) are presented. The linearity in the distribution suggest a genetic additive model followed by SNPs rs1712517, rs11172113, rs11906854 and rs4803455 influencing the levels of expression of the USMG5, STAT6, CPNE1 and BCKDHA genes respectively

## Discussion

As with other complex diseases, published GWAS confirm that common risk variants which individually explain a large proportion of migraine heritability do not exist. Instead, multiple risk variants with small and cumulative effects on the phenotype are most likely to explain the heritability of migraine.

Consistent with this hypothesis, we found that a polygenic risk score computed based on SNPs identified in published GWAS was associated with migraine case-control status in the isolated population of Norfolk Island. Our results also support a regulatory role for these SNPs on the expression of mitochondrial, immunological and hormonal genes. As the number of bona fide migraine risk SNPs

increases, a polygenic score can potentially be used to predict the risk of migraine and eventually it could represent a predictor with better discrimination properties between different sub-classifications of the disorder. This methodology, fitting associated and non-associated SNPs simultaneously into the polygenic model, have been applied successfully in the past to explain a large proportion of the heritability for human height (Yang, Benyamin et al. 2010), schizophrenia and bipolar disorder (International Schizophrenia, Purcell et al. 2009). Similarly, more simplistic models where only associated variants from independent case-controls association studies are included were able to predict coronary heart disease (Morrison, Bare et al. 2007), and prostate cancer risk (Aly, Wiklund et al. 2011). This is the first time than the later methodology has been applied to support a polygenic model in migraine.

The score analysis provides evidence for the existence of a polygenic influence on susceptibility of migraine; however, it provides little guidance as to which of the SNPs included in the polygenic score represent true migraine risk factors in the Norfolk Island population. Results from our gene expression analysis identified 4 SNPs that regulate the expression of a nearby gene, which provides further independent support for these variants. The most significant association was observed between rs1712517 and *USMG5* (Up-regulated during skeletal muscle growth) expression, which is consistent with results reported in a previous large GWAS of gene expression (Westra, Peters et al. 2013). Earlier studies in lymphoblastoid cell lines (Stranger, Nica et al. 2007, Veyrieras, Kudaravalli et al. 2008) and in circulating monocytes (Zeller, Wild et al. 2010) also identified rs1712517 as an eQTL SNP for the *USMG5* gene. Interestingly, the *USMG5* gene is highly expressed in mitochondria where it plays a critical role in maintaining the ATP synthase population (Safran, Dalah et al. 2010). Mitochondrial dysfunction can occur as a result of the reduce capacity to produce ATP, and this impairment in energy supply can affect the function of neurons and other cells, increasing the risk for neurological disorders (Alvarez, Corao et al. 2008). *USMG5* also lies in a genomic region previously associated with schizophrenia (Ripke, O'Dushlaine et al. 2013). In our study, the allele that increased USMG5 expression (G) was associated with decreased migraine risk.

Another notable association was observed between rs11172113 and the expression of the *STAT6* gene, also consistent with previous reports (Stranger, Nica et al. 2007, Westra, Peters et al. 2013). The protein encoded by the *STAT6* (Signal Transducer and Activator of Transcription 6) gene is a member of the STAT family of transcription factors which carries out a dual function: signal transduction and activation of transcription. It is also involved in IL4 (interleukin-4) and IL3 (interleukin-3) mediated signalling. Cytokines are involved in a number of cellular processes including apoptosis, chemotaxis and cell proliferation and they have been associated with neuronal damage and pain in response to particular cellular states, such as hypothermia and hypoxia. The role of cytokines in the neuro-inflammatory response and its influence in the development of migraine has been widely studied (Stuart, Maher et al. 2013).

On the other hand, we discovered a previously unrecognised eQTL for the *BCKDHA* gene, rs4803455, which is located 65Kb upstream of the transcription start site. The allele that increased gene expression levels (A allele, Figure 4) was associated with increased migraine risk (Supplemental Table 1). BCKD is a mitochondrial multienzyme complex comprised of three catalytic components, one of them, a branched chain α-ketoacid decarboxylase subunit (E1) is encoded by the *BCKDHA* gene (D.T. Chuang 2001). The gene is involved in the metabolism of the essential branched-chain amino acids (BCAAs) leucine, valine, and isoleucine and other mutations have been implicated in the development of maple syrup urine disease, an autosomal recessive metabolic disorder (Wang, Qi et al. 2012).

Finally, the biggest limitation faced by this and other neurological studies (Borovecki, Lovrecic et al. 2005, Vawter, Atz et al. 2006, Seifuddin, Pirooznia et al. 2013) is the use of expression profiles from peripheral blood samples. The reasons behind this fact are the inconsistency of gene expression levels all through the brain caused by the vast amount of cell types (Khaitovich, Muetzel et al. 2004) and the technical inconvenience in collecting brain tissue samples in post-mortem (Liu 2011). This contrasts with the accessibility of peripheral blood tissue what in turn, facilitates the acquisition of a bigger sample size. Interestingly, a recent study by McKenzie et al. (McKenzie, Henders et al. 2014), described the eQTLs overlapping in brain regions and blood, supporting the use of blood samples when conditions do

not allow the targeting of specific disease tissues. However, cell types specific to the pathophysiology of the investigated disorder should be used whenever possible to perform transcription analysis.

In conclusion, we provide evidence for a significant polygenic component to migraine risk in the isolated population of the Norfolk Island. Our results also point to two putative migraine risk genes that affect mitochondrial function, *USMG5* and *BCKDHA,* which might represent novel biological targets for migraine treatment.

## Conclusions

Results from this study provide evidence for the existence of a polygenic influence in migraine driven by gene variants affecting mitochondrial, immunological and hormonal gene mRNA levels in the cellular environmental. Additionally, we have replicated eQTLs from previous studies further validating our approach. We have also reported four eQTLs (rs1712517-*USMG5*; rs11172113-*STAT6*; rs11906854-*CPNE1*; rs4803455- *BCKDHA*) interacting with genes relevant to the migraine pathophysiology that were significant at a study level. The rs4803455-*BCKDHA* is a novel eQTL reported for the first time in this study. Further studies are needed to fully understand the role of these variants in the development of migraine. Thus, this study open doors to the investigation of novel biological targets for migraine treatment to be considered in future studies.

Conflict of Interest: The authors declare that they have no conflict of interest.

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**Table 1. eQTL analysis.** Results from a logistic regression analysis. Alleles were coded as 0, 1 and 2 according to the number of copies of a reference allele (A1). Allele frequency of A1 is indicated in the minor allele frequency (MAF) column; Corrected P-values by a permutation test are indicated: the Gene P-value (G_Pvalue), locus P-value (L_P-value) and study P-value(S_P-value) were calculated by dividing the number of times P-value ≤ Raw P-value (R_P-value) by the total permutations (1000) in the same gene, the same locus and in the total study, respectively. Odd Ratio (OR) and their respective 95 % Confidence Intervals (CI 95%) are calculated for the minor allele (A1). Finally, we show the risk allele reported by every GWAS in the "GWAS risk allele" column.

| | | | | | Association with gene-expression | | | Association with migraine risk | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **SNP** | **A1** | **MAF** | **Probe** | **Gene** | **Asymptotic P-value** | **Empirical P-value after locus-wide correction** | **Empirical P-value after study-wide correction** | **OR** | **CI 95%** | **GWAS Risk Allele** |
| rs1712517 | G | 0.4462 | ILMN_1773313 | USMG5 | 0.00003 | <0.001 | 0.012 | 0.83 | 0.76-0.90 | T |
| rs11172113 | C | 0.4104 | ILMN_1763198 | STAT6 | 0.00008 | 0.001 | 0.033 | 0.87 | 0.81-0.93 | T |
| rs11906854 | G | 0.1147 | ILMN_2276000 | CPNE1 | 0.0001 | <0.001 | 0.044 | 0.82 | 0.71-0.89 | G |
| rs4803455 | A | 0.4588 | IILMN_1670841 | BCKDHA | 0.0001 | 0.003 | 0.044 | 0.8 | 0.71-0.89 | C |
| rs11906854 | G | 0.1147 | ILMN_1670841 | CPNE1 | 0.0004 | 0.004 | 0.16 | 0.79 | 0.70-0.90 | G |
| rs3094117 | G | 0.3297 | ILMN_1721113 | HLA-C | 0.0004 | 0.016 | 0.16 | 1.46 | 1.18-1.80 | T |
| rs7085387 | G | 0.233 | ILMN_1715661 | TFAM | 0.0006 | 0.004 | 0.26 | 1.17 | 1.07-1.28 | A |
| rs2076054 | C | 0.276 | ILMN_1715963 | FBXO7 | 0.001 | 0.014 | 0.44 | 1.25 | 1.08-1.45 | C |
| rs3094117 | G | 0.3297 | ILMN_1716922 | DHX16 | 0.002 | 0.082 | 0.82 | 0.93 | 0.86-0.97 | T |
| rs3094117 | G | 0.3297 | ILMN_2101885 | TUBB | 0.002 | 0.082 | 0.82 | 0.91 | 0.86-0.97 | T |
| rs10037055 | T | 0.2572 | ILMN_2278850 | RAB24 | 0.002 | 0.082 | 0.82 | 0.93 | 0.89-0.97 | G |
| rs10037055 | T | 0.2572 | ILMN_1714393 | RAB24 | 0.003 | <0.001 | 1.23 | 1.08 | 1.02-1.14 | G |
| rs11906854 | G | 0.1147 | ILMN_1795317 | SCAND1 | 0.003 | 0.047 | 1.23 | 1.17 | 1.05-1.30 | G |
| rs2274316 | C | 0.3065 | ILMN_2126239 | SMG5 | 0.009 | 0.366 | 3.67 | 1.07 | 1.01-1.13 | C |
| rs11906854 | G | 0.1147 | ILMN_2411963 | RBM39 | 0.013 | 0.21 | 5.51 | 1.12 | 1.02-1.22 | G |
| rs2274316 | C | 0.3065 | ILMN_1696749 | LMNA | 0.024 | 0.94 | 11.76 | 1.09 | 1.01-1.17 | C |
| rs4478147 | G | 0.4821 | ILMN_1815780 | MAPK10 | 0.033 | 0.13 | 15.93 | 0.94 | 0.90-0.99 | G |

**Table 2. Biological function of eQTL genes.** Name and biological function of genes correlated with at least one SNP in our study. Source: Gene Cards (Doniger 2010).

| SNP eQTL | Gene | Name | Function |
|---|---|---|---|
| rs1712517 | USMG5 | Upregulated During Skeletal Muscle Growth | Plays a critical role in maintaining the ATP synthase population in mitochondria |
| rs11172113 | STAT6 | Signal Transducer And Activator Of Transcription 6, Interleukin-4 | It forms homo- or heterodimers that translocate to the cell nucleus where they act as transcription activators. |
| rs11906854 | CPNE1 | Copine 1 | May function in membrane trafficking. Exhibits calcium depend phospholipid binding properties. |
| rs4803455 | BCKDHA | Branched Chain Keto Acid Dehydrogenase E1 | The branched-chain alpha-keto dehydrogenase complex catalyzes the overall conversion of alpha-keto acids to acyl-coa and CO(2). It contains multiple copies of three enzymatic components: branched-chain alpha-keto acid decarboxylase (E1), lipoamide acyltransferase (E2) and lipoamide dehydrogenase (E3) |
| rs3094117 | HLA-C | Major Histocompatibility Complex I | Involved in the presentation of foreign antigens to the immune system |
| rs7085387 | TFAM | Transcription Factor A | Binds to the mitochondrial light strand promoter and functions in mitochondrial transcription regulation. Required for accurate and efficient promoter recognition by the mitochondrial RNA polymerase. |
| rs2076054 | FBXO7 | F BOX Protein | E3 ubiquitin protein ligase complex which mediates the ubiquitination and subsequent proteasomal degradation of target proteins. |
| rs3094117 | DHX16 | DEAH (Asp-Glu-Ala-His) Box Polypeptide 16 | ATP binding RNA helicase involved in re-mRNA splicing |
| rs3094117 | TUBB | Tubulin Beta Class 1 | Constituents of microtubules. It binds two moles of GTP associated with cortical displasia and other brain malformations. |
| rs10037055 | RAB24 | RAS oncogene family | Involved in autophagy related processes |
| rs11906854 | SCAND1 | SCAN Domain Containing 1 | May regulate transcriptional activity |
| rs2274316 | SMG5 | SMG5 Nonsense Mediated | mRNA decay factor |
| rs11906854 | RBM39 | RNA Binding Motif Proteins | Transcriptional coactivator for steroid nuclear receptors esr1 er-alpha and esr2. |

| SNP eQTL | Gene | Name | Function |
|---|---|---|---|
| rs2274316 | LMNA | Lamin A/C | Lamins are components of the nuclear lamina, a fibrous layer on the nucleoplasmic side of the inner nuclear membrane, which is thought to provide a framework for the nuclear envelope and may also interact with chromatin. |
| rs4478147 | MAPK10 | Mitogen Activated Protein Kinase 10. | Role in neuronal differentiation growth and apoptosis. Citokine activation |

Common Polygenic Variation Contributes to Risk of Migraine in the Norfolk Island Population. Human Genetics.

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**Supplementary Table 1.** Fifty-one SNPs were included in the multi-marker scoring analysis. Here, we show the general information provided for every SNP from previous GWASs. From left to right, the columns show the SNP name, chromosomal region, chromosomal position, the associated trait (MO: Migraine without Aura; MA: Migraine with Aura), Associated Allele (Assoc Alle), Risk Allele Frequency (RAF), P-value, Odd Ratio (OR), 95% Confidence Interval (95%CI), Study were the SNP was reported and the platform used to perform the SNP array.

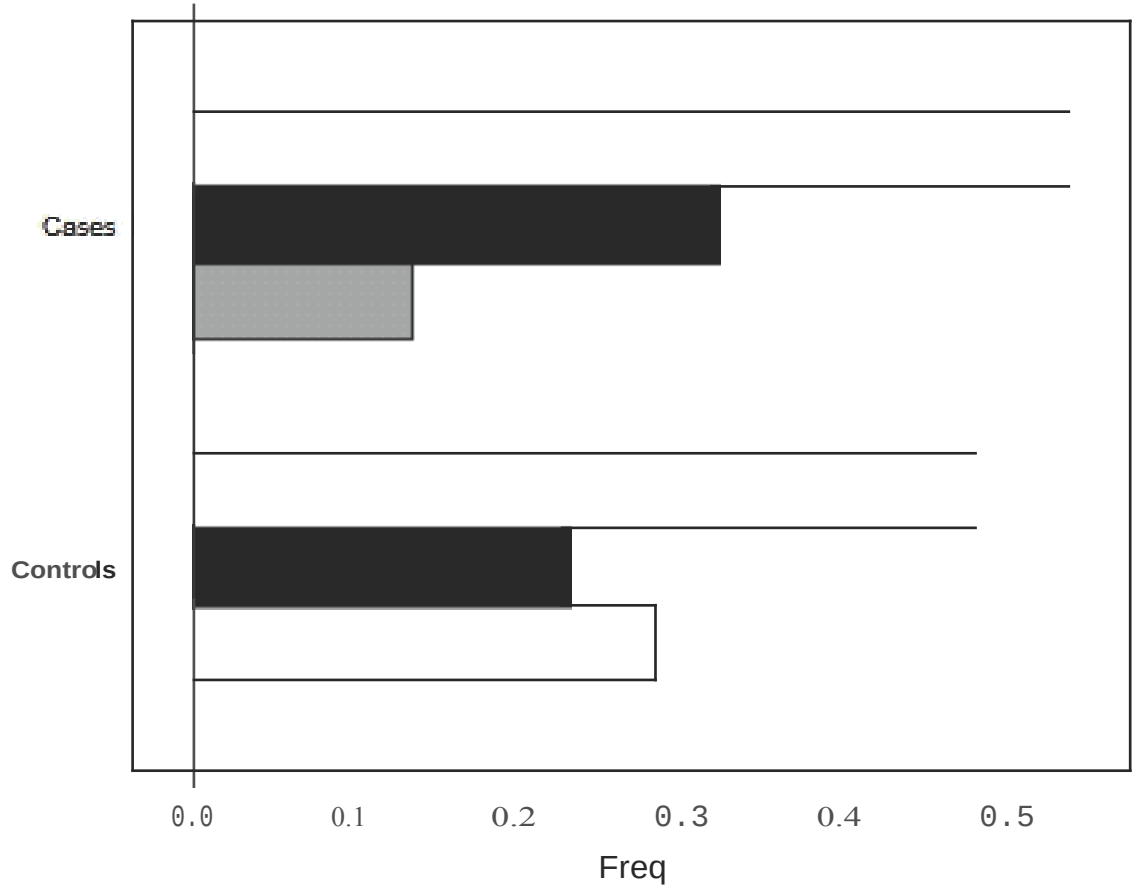
| SNP | Region | Chr. Position | Trait | Assoc Alle | RAF | P-val | OR | 95% CI | Study | Platform |
|---|---|---|---|---|---|---|---|---|---|---|
| rs10037055 | 5q35.3 | 177264278 | Migraine MO | G | 0.83 | 5.00E-06 | 1.14 | [1.08-1.19] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs10166942 | 2q37.1 | 233916448 | Migraine | T | 0.82 | 1.00E-12 | 1.28 | [1.19-1.37] | Freilinger T | Illumina [1,246,388] |
| rs10820447 | 9q22.32 | 96369762 | Migraine MA | T | 0.16 | 6.00E-06 | 1.16 | [1.09-1.23] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs10826566 | 10p12.1 | 29075768 | Migraine MA | A | 0.17 | 4.00E-06 | 1.16 | [1.09-1.23] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs10997517 | 10q21.3 | 67120045 | Migraine MO | C | 0.23 | 6.00E-06 | 1.14 | [1.08-1.21] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs11172113 | 12q13.3 | 57133500 | Migraine | T | 0.57 | 4.00E-19 | 1.11 | [1.09-1.14] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs11594111 | 10p13 | 14903407 | Migraine | G | 0.14 | 1.00E-07 | 1.09 | [1.06-1.12] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs11636768 | 15q25.3 | 87152280 | Migraine | A | 0.15 | 5.00E-07 | 1.25 | [NR] | Ligthart L | Affymetrix, Illumina & Perlegen [~2.5 m] |

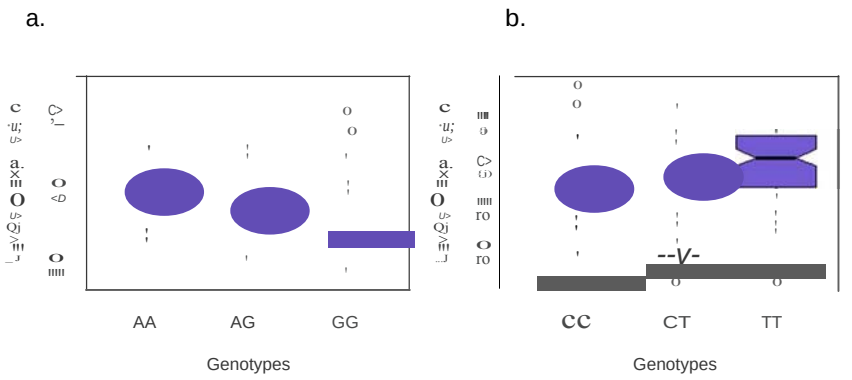
| SNP | Region | Chr. Position | Trait | Assoc Alle | RAF | P-val | OR | 95% CI | Study | Platform |
|---|---|---|---|---|---|---|---|---|---|---|
| rs11726563 | 4p12 | 46821617 | Migraine | A | 0.84 | 8.00E-06 | 1.16 | [1.09-1.23] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs11777116 | 8p21.2 | 24186788 | Migraine | T | 0.08 | 6.00E-08 | 1.27 | [1.17-1.39] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs11906854 | 20q11.22 | 35795712 | Migraine | G | 0.14 | 7.00E-06 | 1.17 | [1.09-1.26] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs12282928 | 11p11.2 | 48310476 | Migraine | A | 0.77 | 9.00E-06 | 1.14 | [1.08-1.2] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs12365397 | 11p12 | 43214511 | Migraine | A | 0.68 | 9.00E-06 | 1.05 | [1.03-1.09] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs12454023 | 18q21.31 | 58342372 | Migraine MA | T | 0.5 | 8.00E-07 | 1.12 | [1.08-1.18] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs13263568 | 8q13.3 | 71535183 | Migraine | G | 0.09 | 2.00E-06 | 1.1 | [1.06-1.14] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs1364402 | 7q33 | 136899616 | Migraine MA | T | 0.91 | 4.00E-06 | 1.19 | [1.11-1.28] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs140174 | 22q11.23 | 23580796 | Migraine | G | 0.26 | 8.00E-06 | 1.08 | [NR] | Ligthart L | Affymetrix, Illumina & Perlegen [~2.5 m] |
| rs1485395 | 12q13.13 | 53601293 | Migraine MO | C | 0.16 | 7.00E-06 | 1.13 | [1.07-1.19] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs1712517 | 10q24.33 | 103273258 | Migraine | T | 0.48 | 9.00E-06 | 1.13 | [1.07-1.17] | Freilinger T | Illumina [1,246,388] |
| rs17301853 | 1q25.1 | 174583673 | Migraine MO | C | 0.88 | 7.00E-06 | 1.19 | [1.1-1.28] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs1835740 | 8q22.1 | 97154685 | Migraine | A | 0.21 | 2.00E-11 | 1.18 | [1.13-1.24] | Anttila V | Illumina [429,912] |
| rs1861960 | 7q36.3 | 155492440 | Migraine | T | 0.2 | 6.00E-06 | 1.07 | [1.04-1.10] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs2076054 | 22q12.3 | 32436887 | Migraine MA | C | 0.26 | 8.00E-06 | 1.12 | [1.07-1.18] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs2274316 | 1q22 | 156476450 | Migraine | C | 0.36 | 1.00E-08 | 1.07 | [1.05-1.10] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs2506155 | 10p11.22 | 33214251 | Migraine | A | 0.15 | 3.00E-06 | 1.08 | [1.04-1.11] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs2651899 | 1p36.32 | 3167148 | Migraine | C | 0.41 | 4.00E-14 | 1.09 | [1.07-1.11] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs2723279 | 12q24.23 | 117835066 | Migraine | G | 0.69 | 5.00E-06 | 1.06 | [1.03-1.09] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs2877098 | 7p14.1 | 41703696 | Migraine MO | C | 0.66 | 2.00E-06 | 1.11 | [1.06-1.16] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs2946505 | 8p22 | 12953643 | Migraine | A | 0.78 | 9.00E-06 | 1.06 | [1.03-1.09] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs3094117 | 6p21.33 | 30769709 | Migraine MO | T | 0.77 | 2.00E-06 | 1.12 | [1.06-1.18] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs378363 | 9p23 | 9020223 | Migraine | A | 0.77 | 8.00E-06 | 1.14 | [1.08-1.2] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs400824 | 8q21.13 | 80445467 | Migraine | A | 0.7 | 9.00E-06 | 1.12 | [1.06-1.19] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs4379368 | 7p14.1 | 40426601 | Migraine MO | T | 0.11 | 1.00E-09 | 1.11 | [1.08-1.15] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs4478147 | 4q21.3 | 86552623 | Migraine | G | 0.47 | 2.00E-06 | 1.12 | [1.07-1.18] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs4493873 | 8q21.3 | 91063415 | Migraine | C | 0.64 | 5.00E-06 | 1.14 | [1.08-1.2] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs4803455 | 19q13.2 | 41345604 | Migraine | C | 0.5 | 8.00E-07 | 1.05 | [1.03-1.08] | Anttila V | Affmetrix & Illumina [~2.3 million] |

| SNP | Region | Chr. Position | Trait | Assoc Alle | RAF | P-val | OR | 95% CI | Study | Platform |
|---|---|---|---|---|---|---|---|---|---|---|
| rs4880487 | 10p15.3 | 1200943 | Migraine | T | 0.25 | 3.00E-06 | 1.06 | [1.04-1.09] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs4909945 | 11p15.4 | 10652192 | Migraine | C | 0.67 | 2.00E-07 | 1.06 | [1.04-1.09] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs516243 | 1p36.22 | 10690375 | Migraine | A | 0.49 | 9.00E-06 | 1.11 | [1.06-1.17] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs543844 | 6p21.1 | 44457063 | Migraine | G | 0.34 | 3.00E-06 | 1.06 | [1.03-1.08] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs6478241 | 9q33.1 | 116490350 | Migraine | A | 0.38 | 1.00E-09 | 1.16 | [1.11-1.22] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs6479874 | 10q11.23 | 51029595 | Migraine | T | 0.14 | 3.00E-07 | 1.09 | [1.05-1.12] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs6583954 | 10q23.33 | 94774506 | Migraine | T | 0.14 | 4.00E-06 | 1.08 | [1.04-1.11] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs6756590 | 2q35 | 216343848 | Migraine | T | 0.56 | 1.00E-06 | 1.14 | [1.08-1.2] | Freilinger T | Illumina [1,246,388] |
| rs6790925 | 3p24.1 | 30438593 | Migraine | T | 0.38 | 2.00E-08 | 1.15 | [1.10-1.21] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs705162 | 10q26.13 | 123492159 | Migraine | A | 0.26 | 3.00E-06 | 1.06 | [1.04-1.09] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs7068341 | 10p13 | 16592300 | Migraine | T | 0.12 | 2.00E-06 | 1.09 | [1.05-1.12] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs7085387 | 10q21.1 | 58444842 | Migraine MO | A | 0.8 | 2.00E-06 | 1.14 | [1.08-1.19] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs7718446 | 5q32 | 146369972 | Migraine MO | A | 0.72 | 4.00E-06 | 1.11 | [1.06-1.16] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs9349379 | 6p24.1 | 12903725 | Migraine | A | 0.6 | 5.00E-08 | 1.08 | [1.04-1.1] | Anttila V | Affmetrix & Illumina [~2.3 million] |
| rs973009 | 19q13.2 | 38683692 | Migraine MA | A | 0.87 | 4.00E-06 | 1.18 | [1.1-1.27] | Anttila V | Affmetrix & Illumina [~2.3 million] |

Controls
Cases
Migraine

0
10
20
30
40
50
0.016
0.018
0.020
0.022
0.024
0.026
0.028
Score


Cases
Controls
0.0
0.1
0.2
0.3
0.4
0.5
Freq


a.
b.
AA
AG
GG
Genotypes
CC
CT
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Genotypes
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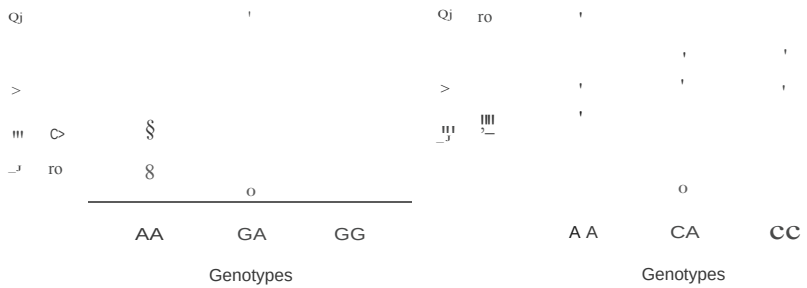
AA
GA
GG
Genotypes
A A
CA
CC
Genotypes